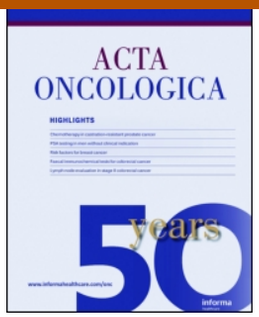

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ORIGINAL ARTICLE

Menopausal hormone therapy and biliary tract cancer: a population-based matched cohort study in Sweden

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ABSTRACT

Background: This study tested the hypothesis that contemporary menopausal hormonal therapy (MHT) increases the risk of biliary tract cancer. The risk of cancer of the biliary tract (gallbladder and extra-hepatic bile ducts) may be increased following estrogen exposure.

Material and methods: This was a nationwide population-based matched cohort study in Sweden. Data from the Swedish Prescribed Drug Register identified all women exposed to systemic MHT in 2005–2012. Group-level matching (1:3 ratio) was used to select women unexposed to MHT from the same study base, matched for history of delivery, thrombotic events, hysterectomy, age, smoking- and alcohol related diseases, obesity, and diabetes. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results: Comparing 290,186 women exposed to MHT with 870,165 unexposed, MHT did not increase the OR of biliary tract cancer. The OR of gallbladder cancer was rather decreased in MHT users (OR 0.58, 95% CI 0.43–0.79), but this association became attenuated and statistically non-significant after adjusting for gallstone disease (OR 0.84, 95% CI 0.60–1.15). The OR of extra-hepatic bile duct cancers was 0.83 (95% CI 0.61–1.15). There were no clear differences when the analyses were stratified for estrogen or estrogen/progestogen combinations. MHT increased the risk of gallstone disease (OR 6.95, 95% CI 6.64–7.28).

Conclusions: Contemporary MHT does not seem to increase the risk of biliary tract cancer. The decreased risk of gallbladder cancer may be explained by the increased use of surgery for symptomatic gallstones in MHT users.

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Introduction

Biliary tract cancers comprising cancers of the gallbladder and the extra-hepatic bile ducts, including the ampulla, are highly lethal [1]. Gallbladder cancer and cancers of the extra-hepatic bile ducts share many epidemiological characteristics and risk factors such as primary sclerosing cholangitis, obesity and diabetes. There are, however, some important differences [1]. Most notably, gallbladder cancer occurs more frequently in women, whereas extra-hepatic tumors are more evenly distributed between the sexes [2]. The reason for the sex difference in gallbladder cancer is not entirely understood, although the association with gallstone disease is a potential explanation [3]. Gallstone disease is more common in women and is associated with estrogen exposure [4]. Thus, gallstone disease seems to be related to both estrogen exposure and BTC. Furthermore, some studies investigating a potential hormonal hypothesis, have suggested an increased risk of gallbladder cancer with increasing parity and other reproductive factors, both used as proxies for endogenous hormone exposure [5–7]. However, the risk of BTC following exogenous estrogen exposure has rarely been studied. Menopausal hormone therapy (MHT) is indicated to alleviate vaso-motor symptoms, osteoporosis, and vaginal atrophy in menopausal women [8,9]. An increased risk of breast and endometrial cancer following MHT has been reported [8,10,11]. Additionally, some studies have indicated decreased risks of some gastro-intestinal cancers following MHT exposure, particularly adenocarcinoma of the esophagus, stomach, and colon [11,12]. The evidence of an association between MHT and BTC is inconsistent. Some studies have reported an increased risk of BTC in MHT exposed women, whereas other studies have shown opposing results

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[13–15]. Previous studies have been small (i.e., fewer than 30 women with cancer) and have seldom been population-based, introducing a risk of chance errors and selection bias, respectively. Furthermore, some previous studies have not distinguished gallbladder cancer from other types of biliary tract cancer or even liver cancers, making results difficult to interpret [13].

Estrogen and progesterone receptors are expressed in both normal and dysplastic biliary tract tissue and *in vitro* studies have shown that estrogen exposure increases cancer growth, whereas estrogen receptor antagonists can inhibit cancer growth in biliary tract cancer cell lines [16–18]. Thus, there is biological support for the hypothesis that female sex hormone exposure increases the risk of BTC.

This study was prompted by the unclear associations between sex hormone exposure and BTC risk. A population-based cohort study was undertaken to test whether the risk of BTC is increased in contemporary MHT users compared with non-users in Sweden.

Material and methods

Study design

This was a nationwide Swedish population-based, matched cohort study investigating the relative risk of BTC following contemporary MHT, described in more detail elsewhere [19–22]. Swedish women aged 40 years or older who exposed to MHT between 1 July 2005 and 31 December 2012 were considered ever-users. Study subjects were identified through the Swedish Prescribed Drug Register. Unexposed control subjects were matched women without MHT drug prescriptions from the same source population and during the same time period as those exposed. Newly diagnosed BTC was assessed by linkage to the Swedish Cancer Register. Women with a history of cancer prior to the start of the study were excluded. To assess a potential mediating effect of gallstones, this study also investigated the association between MHT and gallstone disease. This was performed using gallstone disease as the outcome in a separate analysis, and also as a covariate in the analyses of BTC. All potential confounders were assessed by record linkage. The Regional Ethics Review Board in Stockholm, Sweden, approved the study.

Data sources and data collection

The Swedish Prescribed Drug Register was established in July 2005. The register includes all prescribed and dispensed drugs in Sweden [23]. The register is maintained by the National Board of Health and Welfare and data are transferred from pharmacies on a monthly basis. The register covers the whole of Sweden and is 99.7% complete [23]. Exposure data, including Anatomical Therapeutic Chemical (ATC) codes, dates of drug dispensation, and mode of administration were collected from this register.

The Swedish Cancer Register, established in 1958, includes information on newly diagnosed cancers in Sweden and is of excellent overall quality, but may be less complete concerning BTC specifically [24,25]. Data on cancer diagnosis, anatomical location and histological subtype were extracted from this register.

The Swedish Causes of Death Register was used to establish date of death used for censoring. The register was started in 1961 and is of high overall quality, with 100% completeness in recording of deaths in Sweden [26].

The Swedish Patient Register was established in 1964 and contains information on diagnoses and surgical procedures. The register is 100% complete from 1987 onwards and is of high overall accuracy for diagnoses and surgical procedures [27,28]. The register was used to collect information on past or current medical conditions, patient data, presence of gallstone disease, previous hysterectomy (surgical removal of the uterus), and cholecystectomy (surgical gallbladder removal).

The personal identity number, assigned to all Swedish residents, was used for accurate data collection of all individuals from the registers [29].

Matching procedure

Group-level matching (1:3 ratio) was used to select a cohort of unexposed women from the same study base, exactly matched for history of delivery (yes or no), thrombotic events (yes or no), and hysterectomy (yes or no). This procedure created eight strata in which exact matching was performed for each variable. Furthermore, unexposed subjects within each stratum were matched for age (year of birth), diabetes (yes or no), obesity (yes or no), smoking-related disease (yes or no), and alcohol-related disease (yes or no) using the nearest neighbor strategy [30]. Status of the matching variables was based on data retrieved from the Patient Register.

Follow-up

The cohort was followed up until BTC diagnosis, death, or end of study period, whichever occurred first. Additionally, cohort members diagnosed with cancers other than BTC were censored at the date of cancer diagnosis. For the gallbladder cancer analysis, women with a history of cholecystectomy prior to MHT exposure were excluded from the analyses because these individuals were not at risk of developing gallbladder cancer.

Exposure

Women of at least 40 years of age, receiving one or more prescriptions of systemic MHT drugs during the study period were considered exposed. MHT drugs were defined by the ATC codes: 'G03C' (estrogens), 'G03D' (progestins), and 'G03F' (estrogens and progestins in combination). Only oral and transdermal drugs were considered since these represent systemic treatment. Users of progestins only were excluded, because of the estrogen-based hypothesis of this study. MHT is not available as over-the-counter drugs in Sweden.

Outcome

The primary outcome was BTC diagnosis identified in the Swedish Cancer Register. The ICD-10 codes C23.9 and C24 were used to identify gallbladder cancer and cancer of the extra-hepatic bile ducts, respectively. Because of the similarities in etiology, ampullary cancers, and cancers of the extra-hepatic bile ducts were grouped into one category; extra-hepatic bile duct cancers. Gallbladder cancer and extra-hepatic bile duct cancers were analyzed separately. Furthermore, only adenocarcinomas were included to avoid potential bias by tumor biology differences. Gallstone disease was a secondary outcome and the association with MHT was evaluated in separate analyses.

Statistical analyses

The risk of BTC comparing women exposed to MHT with those unexposed to MHT was assessed using multivariable conditional logistic regression adjusted for all eight matching variables and osteoporosis providing odds ratios (OR) with 95% confidence intervals (CI) since the group-matching procedure neutralized the effect of follow-up time, and no substitute date was assigned for the never-users to assess the duration of follow-up [22]. MHT exposure was categorized as a binary variable (ever or never) and the analyses were stratified according to the type of MHT regimen, either estrogen only or estrogen and progestogen combinations. As well as the matching procedure described above, we also adjusted for all matching variables in a multivariable model using the same categories as presented above. Additionally, osteoporosis was added as a potential confounder to further limit the effect of confounding by indication.

For gallbladder cancer, additional analyses were performed to evaluate a potentially mediating role of gallstone disease. First, we excluded subjects with gallstone disease diagnosed prior to the start of the study to evaluate any influence of gallstone disease on the association between MHT and gallbladder cancer risk. Second, a model in which gallstone disease was the primary outcome was fitted to evaluate the risk of gallstone associated with MHT in subjects without any recorded gallstone disease or cholecystectomy prior to the start of the study.

All calculations were performed using the statistical software STATA, version 13.1 (StataCorp. 2013, StataCorp LP, College Station, TX).

Results

Study participants

The study included 1,160,351 women. Of these, 290,186 were exposed to MHT and 870,165 were unexposed. Characteristics of the study participants are presented in Table 1. The mean follow-up time among MHT users was 5.6 years and the median MHT exposure time was 4.9 years. The median age at inclusion was 57 years. The ratio of estrogen-only containing regimens versus combination regimens was close to 1.

Menopausal hormone therapy and risk of gallbladder cancer

In total, 51 and 168 cases of gallbladder cancer were identified in the MHT exposed group and the unexposed group, respectively. The OR of gallbladder cancer was not increased, but rather decreased, when comparing exposed with unexposed women (adjusted OR 0.58, 95% CI 0.43–0.79) (Table 2). The ORs for regimens containing only estrogen and combination regimens were 0.66 (95% 0.46–0.94) and 0.47 (95% CI 0.28–0.78), respectively. After excluding those with a history of gallstones, the decrease became statistical insignificant (adjusted OR 0.84, 95% CI 0.60–1.15); yet the protective effect was more pronounced among those with a history of gallstones (adjusted OR 0.13, 95% CI 0.05–0.36) (Table 2).

Menopausal hormone therapy and risk of extra-hepatic bile duct cancer

In total, 48 cancers were identified in MHT exposed women and 174 cancers were identified in unexposed women. MHT exposure did not increase the risk of extra-hepatic bile duct cancer (OR 0.83, 95% 0.61–1.15). Stratification for MHT regimen showed no statistically significant associations with extra-hepatic bile duct cancers (Table 2).

Table 1. Characteristics of exposed and matched unexposed cohort members.

Variable	Exposed subjects	Unexposed subjects in the matched cohort
Total (%)	290,186 (100)	870,165 (100)
Matching and/or confounding variables (%)		
Delivery	117,861 (40.6)	353,282 (40.6)
Thrombotic events	40,316 (13.9)	120,931 (13.9)
Hysterectomy	51,811 (17.9)	155,138 (17.8)
Diabetes	15,936 (5.5)	48,422 (5.6)
Obesity	5,146 (1.8)	15,526 (1.8)
Smoking	13,601 (4.7)	40,994 (4.7)
Alcohol	7,293 (2.5)	21,455 (2.5)
Osteoporosis	8,256 (2.9)	22,764 (2.6)
Cholecystectomy	25,553 (8.6)	49,818 (5.7)
Gallstone disease	29,102 (10.0)	79,933 (9.2)
MHT subtypes (%)		
Estrogen only	135,988 (46.9)	N/a
Esotrogen/progestin combination	154,198 (53.1)	N/a

Table 2. Menopausal hormone therapy (MHT) and risk of biliary tract cancer by sub-site, expressed as odds ratios (OR) with 95% confidence intervals.

Matched cohort	All MHT OR (95 % CI)	Estrogen only OR (95 % CI)	Estrogen and progestin combination OR (95 % CI)
Gallbladder cancer (all)	0.58 (0.43–0.78)	0.65 (0.46–0.93)	0.46 (0.28–0.78)
Gallbladder cancer (excluding those with prior gallstones)	0.84 (0.60–1.15)	0.91 (0.62–1.35)	0.73 (0.43–1.23)
Gallbladder cancer (if prior history of gallstones)	0.13 (0.05–0.36)	0.21 (0.08–0.58)	–[a]
Cancer of the extra-hepatic bile duct and the Ampulla	0.83 (0.61–1.15)	0.74 (0.48–1.14)	0.97 (0.63–1.51)
Gallstone disease	6.95 (6.64–7.28)	7.18 (6.79–7.59)	6.83 (6.47–7.21)

[a]Estimates could not be calculated since no cases were recorded in the exposed group.

Menopausal hormone therapy and risk of gallstone disease

MHT increased the risk of diagnosed gallstone disease in subjects with no prior history of gallstones (OR 6.95, 95% CI 6.64–7.28) and the increase remained across MHT regimens (Table 2).

Discussion

This study found no support for the hypothesis that contemporary MHT increases the risk of biliary tract cancer. A strong association between MHT exposure and gallstone disease was confirmed.

The strengths of the study are the population-based design and large sample size which minimize selection bias and random error, respectively. This study is, to our knowledge, the largest to address the association between MHT and biliary tract cancer, which made it possible to separately analyze gallbladder cancer and extra-hepatic bile duct cancer. Furthermore, the adjustment for several factors associated with the initiation of MHT and complete follow-up counteract bias from confounding, misclassification, and selection. All data on cancer outcome, confounding factors, and exposure data were recorded independently which counteract information bias. As in propensity-score matching, the group-level matching enabled us to create two groups with a similar probability of receiving MHT, therefore, limiting the risk of selection bias and confounding. This matched cohort design also allowed for both groups, MHT-users and non-users, to be balanced on several known and unknown confounders. Adding the matching variables to the statistical models did not change the results, showing that the matching was successful. This procedure also circumvents the problem with exposure time for never-users (who do not have a start date of exposure). A limitation is the relatively short follow-up time after MHT. It is likely that the effect of MHT on biliary tract cancer carcinogenesis is in some manner time dependent. So, it is conceivable that the follow-up time in the present study was too short for MHT to have exerted a significant role in biliary tract cancer development. In an effort to evaluate duration of MHT, the exposure variable was re-categorized into three categories. However, since there was no information of MHT use prior to the start of the study, these analyses were restricted to 2006 and onwards, reducing the cohort size rather drastically, making the precision limited. Although the information in the Swedish Cancer Register is of high overall quality, a previous study from our group raised concerns about the completeness of the Swedish Cancer Register regarding BTC specifically [24]. However, there is no reason to believe that under-reporting of BTC was associated with MHT and any confounding due to under-reporting should be non-differential. No detailed information about reproductive factors was available in this study. However, it is unlikely that MHT is dependent on reproductive factors such as parity or age at the birth of the first child. Furthermore, the statistical analyses were adjusted for known potential confounding factors such as diabetes and obesity, yet information on body mass index was unavailable. Obesity is a risk factor for gallbladder cancer, and weight may be associated with the age of onset and severity of menopausal symptoms [31] and consequently MHT use, so there may be residual confounding by body weight. Residual confounding by other known or unknown factors cannot be completely excluded, but this error should be limited by the group-level matching on several variables, a design that mimics a randomized trial. Concerning obesity specifically, if exposed women would be more likely to receive MHT, a possible effect of confounding on the results cannot be ruled out. There have been some reports indicating that MHT users are lighter than non-users, thus residual confounding could in part explain the decreased point estimates in this study.

The previous literature addressing the risk of BTC following MHT exposure is scarce. Some previous studies, where no distinction of different tumor locations within the biliary tract was made, have shown conflicting results. One fairly large study (75 cases of BTC) showed no effect of MHT on overall BTC risk [7]. A small study (13 cases of BTC or liver cancer) reported a decreased risk of BTC, but it was not possible to discriminate BTC from liver cancers, making the results difficult to interpret [13]. Furthermore, in previous studies where gallbladder cancer has been studied separately or exclusively, the results have also been conflicting. A case–-control study (31 cases of gallbladder cancer and 3702 controls) found an increased risk of gallbladder cancer following MHT [14]. That study, however, was not population-based and the sample size was limited. In line with the results of this study, a multi-center, case–control study reported a borderline significantly decreased risk of gallbladder cancer (196 cases and 1515 controls) following MHT exposure [28]. Similar results were seen in a previous Swedish study, in which 23 gallbladder cancer cases were identified in a little over 22,000 women exposed to MHT [29]. Gallstone disease was not considered in that study, however.

The results of the present study suggested that MHT reduces the risk of gallbladder cancer, but the association did not remain after adjustment for gallstone disease. Gallstone disease is a risk factor for gallbladder cancer [32,33], and MHT increases the risk of gallstone disease according to the present study and several others [4,34]. The indicator for gallstone disease in the present study will not identify clinically silent gallstone disease. However, it is unknown if the increased risk of gallbladder cancer due to gallstone disease is similar in symptomatic and asymptomatic patients [35,36]. Cholecystectomy for the treatment of symptomatic gallstone disease in women exposed to MHT is a plausible explanation for the reduced risk of gallbladder cancer observed in this study when not adjusting for gallstone disease. Importantly, if the risk of symptomatic gallstone disease after MHT initiation was unrelated to the outcome, no association between MHT and gallbladder cancer would have been observed. Thus, it seems that MHT results in an increased risk of symptomatic gallstone disease in women susceptible to develop gallbladder cancer, i.e., gallstone disease may be an intermediate step in the development of gallbladder cancer in women using MHT.

To our knowledge, only one previous study has investigated the risk of extra-hepatic bile duct cancers after MHT exposure specifically and no association was found [37]. This lack of association is supported by the present study.

In conclusion, the findings of this large population-based cohort study controlling for several potential confounding factors did not support the hypothesis of an increased risk of BTC associated with contemporary MHT.

Disclosure statement

The authors report no conflicts of interest. The work was conducted entirely before author P. K. was employed at his current position in Astra Zenica, so there is no conflict of interest.

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